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Poster presentation

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Protein tyrosine phosphatase nonreceptor 13 (PTPN13) is targeted by human papillomavirus 16 E6 in cervical epithelium

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Objectives

The Post Synaptic density protein-95/Drosophila disc large/Zonula occludens (PDZ) domain binding motif of human papillomavirus (HPV) E6 correlates with malignant transformation for high risk HPV. Recent evidence in our lab has shown that HPV16 E6 binds and degrades PTPN13 in a PDZ binding motif-dependent manner in HPV-positive head and neck squamous cell cancer. The loss of PTPN13 results in invasive growth when combined with Ras expression. The purpose of this study is to investigate PTPN13 expression in normal and malignant cervical epithelial cells, and to evaluate its role in cervical cancer.

Methods

PTPN13 expression was measured by Western blotting in primary cultures of normal and high-risk HPV-infected human cervix and foreskin keratinocytes, in non-tumorigenic HPV 31b positive cells, in HPV positive (CaSki, SiHa) and HPV-negative (C-33A) cervical carcinoma cell lines. Immunohistochemistry with PTPN13 (C-20): sc-1138 antibody was performed on cervical tissue specimens. Primary human cervical cultures and C33A cells were transduced with recombinant adenovirus containing HPV16 E6, E7, and mutant lacking the PDZ domain binding motif (E6Δ146–151). SiHa and Caski cells were transfected with plasmid containing PTPN13. PTPN13 loss was induced in C33A cells using shRNA strategy. Morphologic features, in vitro growth rate, and anchorage independent growth were evaluated. RTPCR was used to measure E6 and E6* expression.

Results

Normal cervical epithelial cells, foreskin keratinocytes and the HPV-negative C-33A cancer cell line express PTPN13. HPV-positive cancer cell lines, as well as cervical and foreskin epithelial cells containing HPV 16, 18, 31 show significant loss of PTPN13 expression. Cells transduced with HPV16 E6Δ146–151/E7 do not survive in vitro compared to cells transduced with HPV E6/E7. PTPN13 loss is E6 PDZ dependent and appears to be associated with integration of E6/E7 into the host genome. Re-establishment of PTPN13 in SiHa and Caski cells decreased colony formation efficiency in soft agar by 21(p = 0.0031) and 68 percent(p = 0.0001) respectively. Loss of PTPN13 via shRNA in C33A cell line increases its colony formation efficiency 133 times (p = 0.0001) in soft agar.

Conclusion

PTPN13 may play an important role as a tumor suppressor in HPV-mediated cervical carcinogenesis. Understanding of this PDZ dependent mechanism may lead to development of targeted molecular therapy against HPV-positive cervical cancer.